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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/939,408	08/24/2001	Roberta K. Yoshida	29479/500NSCA	5670

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EXAMINER	
SAIDHA, TEKCHAND	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/939,408	YOSHIDA ET AL.	
	Examiner	Art Unit	
	Tekchand Saidha	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,11-15,17,19-21,24,25 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,2,5,6,11-13,15,20,21,24,25 and 28* is/are allowed.

6)☒ Claim(s) *3, 14, 17 & 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and arguments filed 12 December 2004, is acknowledged.

2. Claims 1-3, 5-6, 11-15, 17, 19-21, 24-25 & 28 are under consideration in this examination.

3. Applicant's arguments filed as per the amendment cited above have been fully considered but they are not deemed to be persuasive. The reasons are discussed following the rejection(s).

4. Any objection or rejection of record which is not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.

5. ***Continuation of prior application***

Applicants' continuation data, on page 1, lack reference to the patent number. The specification must therefore be amended as follows: This application is a continuation-in-part application of U.S. patent application 09/624,693, filed July 24, 2000, now US Patent 6,355,468 and is a continuation-in-part____.

No response has been received.

6. ***Claim Rejections - 35 USC §112*** (first paragraph)

Enablement

Claims 3, 14, 17 & 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide [SEQ ID NO: 12], encoding a yeast phenylalanine ammonia lyase (PAL) of SEQ ID NO: 13, vector, host cell and method of making the polypeptide recombinantly, does not reasonably provide enablement for any polynucleotide encoding PAL, wherein said PAL is at least 90% identical to SEQ ID NO: 13 or any polynucleotide which is at least 80%, 90% or 95% identical to SEQ ID NO: 12 (nucleotides 37-2196). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The scope of the claims does not commensurate with the enablement provided by the disclosure with regard to the large number of polynucleotides (or nucleic acid) broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide sequence of SEQ ID NO: 12 and the encoded amino acid sequence of SEQ ID NO: 13.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications of DNA of SEQ ID NO: 12 by 5% to 20%, because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting phenylalanine ammonia lyase activity; (B) the general tolerance of phenylalanine ammonia lyase of SEQ ID NO: 12 to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any phenylalanine ammonia lyase residues with an expectation of obtaining the desired enzymatic or biological function; and (D)

the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. This is further supported in the work of Seffernick et al. [J. Bacteriol. Apr. 2001, p. 2405-2410] where melamine Deaminase and Atrazine chlorohydrolase each consists of 475 amino acids, are 98% identical and are yet functionally different. Thus there is high unpredictability associated with respect to modification(s) of the sequence of SEQ ID Nos: 12 or 13 unless guidance is provided in establishing (A) – (D) as discussed above.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of exact nature of phenylalanine ammonia lyase encoding DNA (or polynucleotide) having the desired biological characteristics, as well as vector or host cell constructs is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Applicants' Arguments:

Applicants argue incorrectly that 'Examiner fails to state that all DNA [i.e. modification of DNA of SEQ ID NO: 12 by 5%-20%] within the scope of these claims must encode a polypeptide having PAL activity". However, this is not the case. As can be seen from the previous rejection reproduced here, the PAL activity is recognized.

Applicants further argue that one of ordinary skill could readily prepare numerous DNAs within the scope of each of these claims based upon the degeneracy of the genetic code. For example, substituting each codon for serine with another serine codon would result in significantly different DNAs, but each would still encode same biologically active PAL set out in SEQ ID NO: 13.

Making and using such DNAs would require nothing more than routine experimentation.

Yes, many amino acids are designated or coded by more than one triplet. Degeneracy of the genetic code may also be significant in permitting DNA base composition to vary over a wide range without altering the amino acid sequence of the proteins encoded by the DNA. However, the claims are not directed to any degenerate DNA sequence of SEQ ID NO: 12 or 20. On the contrary, the % homology is directed to the DNA sequence encoding an altered protein sequence [90%, for example] having PAL activity, and such a sequence is not enabled as explained in the enablement rejection.

Applicants further argue that the instant specification is replete with specific modifications and that deletion variants are described comprising deletion of 1-6 residues at the amino or carboxyl terminal ends (specification page 12, lines 8-18). The specification also teaches the preparation of deletion fragments, and which is well known in the art. Citing page 12 (beginning at line 22) Applicants argue that substitution variants are taught; as well as, fusion proteins (page 15, line 25) & mutagenesis of DNA for creating functional derivatives of PAL having altered amino acid sequences can also be prepared by mutating the DNA encoding PAL. Any combination of amino acid deletion, insertion, and substitution may be employed to generate the final construct, such that the final construct possesses the desired activity (page 18, lines 7-17).

Applicants' arguments are considered but not found to be persuasive because the cited teachings are of a general nature with no specific guidance or specific example. No specific mutational modifications of the DNAs in question have been made, in order to support the altered sequences with respect to SEQ ID NO: 12 or 20. The instant specification on page 19 (lines 11-17) recite "mutations designed to alter the activity of PAL may be guided by the introduction of the amino acid residues that are present at homologous

positions in other phenylalanine ammonia lyase proteins (particularly PAL proteins of evolutionarily similar genus/species). It is difficult to predict a priori the exact effect any particular modification, e.g., substitution, deletion, insertion, etc., will have on the biological activity of PAL. However, one skilled in the art will appreciate that the effect will be evaluated by routine screening assays". This is further indicative that no specific examples are described, and no specific guidance provided, and it is difficult to predict the effects of any particular modification. One of skill in the art would therefore be randomly testing various modification(s).

While the relative skill of those in the art of recombinant enzyme is high, the art of protein modification remain unpredictable in view of the nature of invention, the state of the prior art and the inherent unpredictability in the art of mutation, compounded by a lack of specific examples. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, catalysis and in providing the correct three-dimensional spatial orientation of binding and catalytic sites. These or other regions may also be critical determinants of antigenicity or activity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990. Science, Vol.247, pp.1306-1310, especially p.1306, column 2, paragraph 2). However, applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino

acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

The specification on page 14, exemplifies 'conservative substitution'. However, the claims are not directed to conservative substitution(s).

7. Claims 1-2, 5-6 & 11-13, 15, 20-21, 24-25 & 28 are allowed.

8. Claims 3, 14, 17 & 19 are rejected.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha whose telephone number is (571) 272 0940. The examiner can normally be reached on Monday-Friday, between 8.30 am - 5.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272 0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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07 February, 2005